EXHIBIT 3-3

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<223> Dual Labelled Fluorescent TaqMan Probe beta-globin-402T

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AF/1655

Please type a plus sign (+) inside this box → [+]

PTO/SB/21 (6-98)
Approved for use through 09/30/2000. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	09/380,696
Filing Date	November 29, 1999
First Named Inventor	Lo et al.
Group Art Unit	1655
Examiner Name	Jeanine Enewold Goldberg
Total Number of Pages in This Submission: 8	Attorney Docket Number: JAK-PT001

ENCLOSURES *(check all that apply)*

- [x] Fee Transmittal Form
  - [ ] Fee Attached
- [x] Amendment / Response
  - [x] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Assignment Papers *(for an Application)*
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition Routing Slip (PTO/SB/69) and Accompanying Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Small Entity Statement
- [ ] Request for Refund
- [ ] After Allowance Communication to Group
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Additional Enclosure(s) *(please identify below)*:
  - Sequence Listing (3 pgs.) and Diskette

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	C. Frederick Koenig III, Esquire Reg. No. 29,662 Volpe and Koenig, P.C.
Signature	
Date	January 24, 2001

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Box AF, Commissioner for Patents, Washington, D.C. 20231 on this date: January 24, 2001

Typed or printed name	C. Frederick Koenig III, Esquire		
Signature		Date	1/24/01

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be send to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231

Volpe and Koenig, P.C. Revision of

PTO/SB/17 (11-00)
Approved for use through 10/31/2002. OMB 0651-0032
U.S. Patent and Trademark Office; U S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL for FY 2001

Patent fees are subject to annual revision.

TOTAL AMOUNT OF PAYMENT	($) 0.00

Complete if Known	
Application Number	09/380,696
Filing Date	November 29, 1999
First Named Inventor	Lo et al.
Examiner Name	Jeanine. Enewold Goldberg
Group Art Unit	1655
Attorney Docket No.	JAK-PT001 (Formerly SHP-PT048)

METHOD OF PAYMENT

1. ☐ The Commissioner is hereby authorized to charge indicated fees and credit any overpayments to:

Deposit Account Number: 22-0493

Deposit Account Name: Volpe and Koenig, P.C.

☒ Charge Any Deficiency or Credit any Overpayment in the Total Fees Associated with this Communication

☒ Applicant claims small entity status. See 37 CFR 1.27

2. ☐ **Payment Enclosed:**

☐ Check ☐ Credit card ☐ Money Order ☐ Other

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	710	201	355	Utility filing fee	
106	320	206	160	Design filing fee	
107	490	207	245	Plant filing fee	
108	710	208	355	Reissue filing fee	
114	150	214	75	Provisional filing fee	

SUBTOTAL (1) ($) 0.00

2. EXTRA CLAIM FEES

			Extra Claims		Fee from below	Fee Paid
Total Claims	27	- 28	** 0	x	9.00	= 0
Independent Claims	3	- 3	** 0	x	40.00	= 0
Multiple Dependent						=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	18	203	9	Claims in excess of 20
102	80	202	40	Independent claims in excess of 3
104	270	204	135	Multiple dependent claim, if not paid
109	80	209	40	** Reissue independent claims over original patent
110	18	210	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0.00

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for *ex parte* reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	390	216	195	Extension for reply within second month	
117	890	217	445	Extension for reply within third month	
118	1,390	218	695	Extension for reply within fourth month	
128	1,890	228	945	Extension for reply within fifth month	
119	310	219	155	Notice of Appeal	
120	310	220	155	Filing a brief in support of an appeal	
121	270	221	135	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive - unavoidable	
141	1,240	241	620	Petition to revive - unintentional	
142	1,240	242	620	Utility issue fee (or reissue)	
143	440	243	220	Design issue fee	
144	600	244	300	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Processing fee under 37 CFR 1.17(q)	
126	180	126	180	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	710	246	355	Filing a submission after final rejection (37 CFR § 1.129(a))	
149	710	249	355	For each additional invention to be examined (37 CFR § 1.129(b))	
179	710	279	355	Request for Continued Examination (RCE)	
169	900	169	900	Request for expedited examination of a design application	
Other fee (specify)					

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 0.00

SUBMITTED BY

Name (Print/Type)	C. Frederick Koenig III, Esquire	Registration No. (Attorney/Agent)	29,662	Complete (if applicable) Telephone	215-568-6400
Signature				Date	January 24, 2001

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO. Assistant Commissioner for Patents, Washington, DC 20231.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the **PATENT APPLICATION** of:	
	Lo et al.
Application No.:	09/380,696
Filed:	November 29, 1999
For:	NON-INVASIVE PRENATAL DIAGNOSIS
Group:	1655
Examiner:	Jeanine Enewold Goldberg

Our File: JAK-PT001

Date: February 6, 2001

REPLY TO ERROR REPORT

U.S. Patent and Trademark Office
Crystal Mall I
7th Floor
1911 South Clark Street
Arlington, VA 22202

Sir:

This Reply is responsive to the Examiner fax of February 5, 2001 requesting correction of the previously submitted sequence listing per 37 C.F.R. §§1.821-1.825. Please amend the application as follows:

IN THE SPECIFICATION

Please amend the specification by substituting the enclosed paper copy of a Sequence Listing (3 pages.) for the Sequence Listing submitted with Applicants' Supplemental Reply dated January 24, 2001.

REMARKS

Pursuant to the Examiner's fax request, submitted herewith are corrected paper and computer-readable copies of an appropriate "Sequence Listing". The content of the paper and computer-readable copies are the same and include no new matter.

Since an agreement has been reached with respect to the allowability of all pending claims per the Examiner's fax of January 16, 2001, it is respectfully submitted that this case is now in condition for allowance. Reconsideration, entry of this amendment and allowance of the claims is respectfully requested.

Respectfully submitted,

Lo et al.

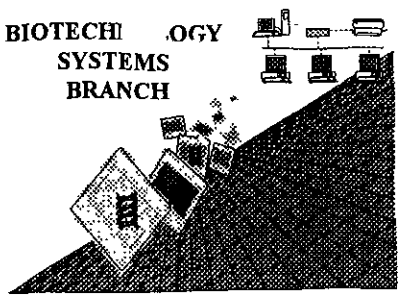
By _____
C. Frederick Koenig III, Esquire
Registration No. 29,662
(215) 568-6400

Volpe and Koenig, P.C.
Suite 400, One Penn Center
1617 John F. Kennedy Boulevard
Philadelphia, PA 19103

CFK/fap

J. Goldberg

#16



RAW SEQUENCE LISTING ERROR REPORT

The Biotechnology Systems Branch of the Scientific and Technical Information Center (STIC) detected errors when processing the following computer readable form:

Application Serial Number: 09/380,696

Source: 1655 RUSH

Date Processed by STIC: 2/5/2001

215-568-6499

THE ATTACHED PRINTOUT EXPLAINS DETECTED ERRORS.
PLEASE FORWARD THIS INFORMATION TO THE APPLICANT BY EITHER:
1) **INCLUDING A COPY OF THIS PRINTOUT IN YOUR NEXT COMMUNICATION TO THE APPLICANT, WITH A NOTICE TO COMPLY or,**
2) **TELEPHONING APPLICANT AND FAXING A COPY OF THIS PRINTOUT, WITH A NOTICE TO COMPLY**

FOR CRF SUBMISSION QUESTIONS, PLEASE CONTACT MARK SPENCER, 703-308-4212.

FOR SEQUENCE RULES INTERPRETATION, PLEASE CONTACT ROBERT WAX, 703-308-4216.
PATENTIN 2.1 e-mail help: patin21help@uspto.gov or phone 703-306-4119 (R. Wax)
PATENTIN 3.0 e-mail help: patin3help@uspto.gov or phone 703-306-4119 (R. Wax)

TO **REDUCE** ERRORED SEQUENCE LISTINGS, **PLEASE** USE THE **CHECKER VERSION 3.0 PROGRAM**, ACCESSIBLE THROUGH THE U.S. PATENT AND TRADEMARK OFFICE WEBSITE. SEE BELOW:

Checker Version 3.0

The Checker Version 3.0 application is a state-of the-art Windows based software program employing a logical and intuitive user-interface to check whether a sequence listing is in compliance with format and content rules. Checker Version 3 0 works for sequence listings generated for the original version of 37 CFR §§1.821 – 1 825 effective October 1, 1990 (old rules) and the revised version (new rules) effective July 1, 1998 as well as World Intellectual Property Organization (WIPO) Standard ST 25.
Checker Version 3.0 replaces the previous DOS-based version of Checker, and is Y2K-compliant. Checker allows public users to check sequence listings in Computer Readable form (CRF) before submitting them to the United States Patent and Trademark Office (USPTO). Use of Checker prior to filing the sequence listing is expected to result in fewer errored sequence listings, thus saving time and money.

Checker Version 3.0 can be down loaded from the USPTO website at the following address:
http://www.uspto.gov/web/offices/pac/checker

SEQUENCE LISTING

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WAINSCOAT, JAMES STEPHEN

<120> NON-INVASIVE PRENATAL DIAGNOSIS

<130> JAK-PT001

<140> US 09/380,696
<141> 1999-11-29

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<151> 1997-03-04

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51

1655

RAW SEQUENCE LISTING DATE: 02/05/2001
PATENT APPLICATION: US/09/380,696 TIME: 12:20:22

Input Set : A:\Isis1.app
Output Set: N:\CRF3\02022001\I380696.raw

Does Not Comply
Corrected Diskette Needed

3 <110> APPLICANT: LO, YUK-MING DENNIS
4 WAINSCOAT, JAMES STEPHEN
6 <120> TITLE OF INVENTION: NON-INVASIVE PRENATAL DIAGNOSIS
8 <130> FILE REFERENCE: JAK-PT001
10 <140> CURRENT APPLICATION NUMBER: US 09/380,696
C-OK 11 <141> CURRENT FILING DATE: 1999-11-29
13 <150> PRIOR APPLICATION NUMBER: GB9621367.3
14 <151> PRIOR FILING DATE: 1997-03-04
16 <160> NUMBER OF SEQ ID NOS: 11
18 <170> SOFTWARE: WordPad

ERRORED SEQUENCES

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115 <223> OTHER INFORMATION: TaqMan Amplification Primer beta-globin-354F
117 <400> SEQUENCE: 9
E--> 118 gtgcacctgactcctgaggaga (24) 22

insert a space between each group of
10 bases in a non-coding sequence, per 1.822 of Sequence Rules — this is a global error, appearing in all sequences

VERIFICATION SUMMARY DATE: 02/05/2001
PATENT APPLICATION: US/09/380,696 TIME: 12:20:23

Input Set : A:\Isis1.app
Output Set: N:\CRF3\02022001\I380696.raw

L:11 M:271 C: Current Filing Date differs, Replaced Current Filing Date
L:118 M:254 E: No. of Bases conflict, LENGTH:Input:24 Counted:22 SEQ:9
L:118 M:252 E: No. of Seq. differs, <211>LENGTH:Input:24 Found:22 SEQ:9

J. Goldberg

RAW SEQUENCE LISTING DATE: 02/15/2001
PATENT APPLICATION: US/09/380,696A TIME: 15:39:25

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Output Set: N:\CRF3\02152001\I380696A.raw

<110> APPLICANT: LO, YUK-MING DENNIS
WAINSCOAT, JAMES STEPHEN
<120> TITLE OF INVENTION: NON-INVASIVE PRENATAL DIAGNOSIS
<130> FILE REFERENCE: JAK-PT001
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RAW SEQUENCE LISTING DATE: 02/15/2001
PATENT APPLICATION: US/09/380,696A TIME: 15:39:25

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Output Set: N:\CRF3\02152001\I380696A.raw

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RAW SEQUENCE LISTING DATE: 02/15/2001
PATENT APPLICATION: US/09/380,696A TIME: 15:39:25

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Output Set: N:\CRF3\02152001\I380696A.raw

139 <400> SEQUENCE: 11
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VERIFICATION SUMMARY DATE: 02/15/2001
PATENT APPLICATION: US/09/380,696A TIME: 15:39:26

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Output Set: N:\CRF3\02152001\I380696A.raw

Notice of Allowability	Application No. 09/380,696	Applicant(s) LO ET AL.	
	Examiner Jeanine A Enewold Goldberg	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *12/27/00; 1/11/01; 1/16/01*.
2. ☒ The allowed claim(s) is/are *1 and 3-28*.
3. ☐ The drawings filed on _____ are acceptable as formal drawings.
4. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☒ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.
5. ☐ Acknowledgement is made of a claim for domestic priority under 35 U S.C. & 119(e).

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application. **THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

6. ☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.

7. ☒ Applicant MUST submit NEW FORMAL DRAWINGS
   (a) ☒ including changes required by the Notice of Draftsperson's Patent Drawing Review(PTO-948) attached
      1) ☐ hereto or 2) ☒ to Paper No. *9*.
   (b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the examiner.
   (c) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No. _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

8. ☐ Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any reply to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE / SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

Attachment(s)

1☐ Notice of References Cited (PTO-892)
2☐ Notice of Informal Patent Application (PTO-152)
3☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
4☒ Interview Summary (PTO-413), Paper No. *14* .
5☐ Information Disclosure Statements (PTO-1449), Paper No. ____.
6☒ Examiner's Amendment/Comment
7☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
8☒ Examiner's Statement of Reasons for Allowance
9☐ Other

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP ~~1800~~ 1600

17/F

gs
1/23/01

EXAMINER'S AMENDMENT

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Frederick Koenig on January 16, 2001.

2. The application has been amended as follows:

F_1

1. (Twice Amended) A [nucleic acid detection] method <u>for detecting a paternally inherited nucleic acid of fetal origin</u> performed on a maternal serum or plasma sample from a pregnant female, which method comprises

<u>amplifying a paternally inherited nucleic acid from the serum or plasma sample and</u>

detecting the presence of a paternally inherited nucleic acid of fetal origin in the <u>sample.</u>

Cancel Claim 2.

F_2

2 3. The method according to Claim [2] 1, wherein the foetal nucleic acid is amplified by the polymerase chain reaction.

In Claim 4, "2" has been amended to - - 1 - -.

F_3

2 5. (Amended) A method <u>for detecting a paternally inherited nucleic acid</u> [of performing a prenatal diagnosis] on a maternal blood sample, which method comprises:

removing all or substantially all nucleated and anucleated cell populations from the blood sample,

<u>amplifying a paternally inherited nucleic acid from the remaining fluid and</u> subjecting the amplified nucleic acid [remaining fluid] to a test <u>for the paternally inherited fetal nucleic acid</u> [indicative of a maternal or fetal condition or characteristic] .

53

26. (Twice Amended) A method for performing a prenatal diagnosis on a maternal blood sample, which method comprises

obtaining a non-cellular fraction of the blood sample

amplifying a paternally inherited nucleic acid from the non-cellular fraction

and performing nucleic acid analysis on the [fraction] amplified nucleic acid to detect paternally inherited fetal nucleic acid.

F4

The first line of the specification has been amended to insert -- This application is the national stage of PCT Application No. PCT/GB98/00690, filed March 4, 1998 under 37 CFR 371 --

F5

3. The following is an examiner's statement of reasons for allowance.

The claims are drawn to a method of detecting paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, by amplifying a paternally inherited nucleic acid from the serum or plasma sample and detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample.

The closest prior art is directed to detecting alterations in plasma DNA for diagnosing and or monitoring the development of DNA (Stroun et al GB 2299166, September 1996). The art also teaches detecting fetal cells in maternal blood and performing diagnostic tests on the blood. However, the art does not teach nor reasonably suggest that nucleic acid of fetal origin is present in maternal serum or plasma.

4. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably

54

accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold Goldberg
January 23, 2001

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP ~~1800~~ 1600

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

NOTICE OF ALLOWANCE AND ISSUE FEE DUE

HM32/0301

C FREDERICK KOENTG III
VOLPE & KOENTG
400 ONE PENN CENTER
1617 JOHN F KENNEDY BOULEVARD
PHILADELPHIA PA 19103

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT		DATE MAILED
09/380,696	11/29/99	027	GOLDBERG, J	1655	03/01/01
First Named Applicant: LO,		35 USC 154(b) term ext. =	0 Days.		

TITLE OF INVENTION: NON-INVASIVE PRENATAL DIAGNOSIS

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1 SHP-1-P048	435-006.000	CR6	UTILITY	NO	$1340.00	06/01/01

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

HOW TO RESPOND TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.
If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is changed, pay twice the amount of the FEE DUE shown above and notify the Patent and Trademark Office of the change in status, or
B. If the status is the same, pay the FEE DUE shown above.

If the SMALL ENTITY is shown as NO:

A. Pay FEE DUE shown above, or

B. File verified statement of Small Entity Status before, or with, payment of 1/2 the FEE DUE shown above.

II. Part B-Issue Fee Transmittal should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B Issue Fee Transmittal should be completed and returned. If you are charging the ISSUE FEE to your deposit account, section "4b" of Part B-Issue Fee Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give application number and batch number. Please direct all communications prior to issuance to Box ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PATENT AND TRADEMARK OFFICE COPY

PTOL-85 (REV. 10-96) Approved for use through 06/30/99. (0651-0033)

PART B—ISSUE FEE TRANSMITTAL

Complete and mail this form, together with applicable fees, to: **Box ISSUE FEE**
Assistant Commissioner for Patents
Washington, D.C. 20231

KG

MAILING INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE. Blocks 1 through 4 should be completed where appropriate. All further correspondence including the Issue Fee Receipt, the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Legibly mark-up with any corrections or use Block 1)

HM32/0301
C FREDERICK KOENIG III
VOLPE & KOENIG
400 ONE PENN CENTER
1617 JOHN F KENNEDY BOULEVARD
PHILADELPHIA PA 19103

Note: The certificate of mailing below can only be used for domestic mailings of the Issue Fee Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing.

Certificate of Mailing

I hereby certify that this Issue Fee Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Box Issue Fee address above on the date indicated below.

C. Frederick Koenig III (Depositor's name)
(Signature)
5/15/01 (Date)

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT		DATE MAILED
09/380,696	11/29/99	027	GOLDBERG, J	1655	03/01/01
First Named Applicant: LO,		35 USC 154(b) term ext. =	0 Days.		

TITLE OF INVENTION: NON-INVASIVE PRENATAL DIAGNOSIS

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
JAK-PT001	435-006.000	C86	UTILITY	NO	620.00	06/01/01

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363). Use of PTO form(s) and Customer Number are recommended, but not required.

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47) attached.

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Volpe and Koenig, P.C.
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)
PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the PTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Isis Innovation Limited

(B) RESIDENCE: (CITY & STATE OR COUNTRY) Oxford, United Kingdom

Please check the appropriate assignee category indicated below (will not be printed on the patent)
☐ Individual ☒ corporation or other private group entity ☐ government

4a. The following fees are enclosed (make check payable to Commissioner of Patents and Trademarks):
☒ Issue Fee
☒ Advance Order - # of Copies 10

4b. The following fees or deficiency in these fees should be charged to:
DEPOSIT ACCOUNT NUMBER
(ENCLOSE AN EXTRA COPY OF THIS FORM)
☐ Issue Fee
☐ Advance Order - # of Copies

The COMMISSIONER OF PATENTS AND TRADEMARKS IS requested to apply the Issue Fee to the application identified above.

(Authorized Signature) (Date) 5/15/01

NOTE: The Issue Fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office.

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending on the needs of the individual case. Any comments on the amount of time required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND FEES AND THIS FORM TO: Box Issue Fee, Assistant Commissioner for Patents, Washington D.C. 20231

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05/21/2001 ABSITTEW1 00000085 09380696
01 FC:242 620.00 DP
02 FC:561 30.00 DP

TRANSMIT THIS FORM WITH FEE

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#18

In the **PATENT APPLICATION** of:

Lo et al.

Application No.: 09/380,696

Filed: November 29, 1999

For: NON-INVASIVE PRENATAL DIAGNOSIS

Group: 1655

Examiner: J. Goldberg

Our File: JAK-PT001

Date: May 16, 2001

Batch No.: C86

Allowed: March 1, 2001

COMMUNICATION ACCOMPANYING FORMAL DRAWINGS

Commissioner for Patents
Washington, D.C. 20231
Attn: Drawing Review Branch

Sir:

Enclosed for filing in connection with the above-identified application are two (2) replacement sheets of formal drawings along with two copies in compliance with the Notice of Allowability dated March 1, 2001. Sheets 3 and 4 are corrected in accordance with amendments made and approved by the Examiner during prosecution.

Respectfully submitted,

Lo et al.

By _____
C. Frederick Koenig III, Esquire
Registration No. 29,662
(215) 568-6400

Volpe and Koenig, P.C.
Suite 400, One Penn Center
1617 John F. Kennedy Boulevard
Philadelphia, PA 19103

CFK/fap

09/380696

WO 98/39474 6258540 PCT/GB98/00690

1/4

Fig.1.

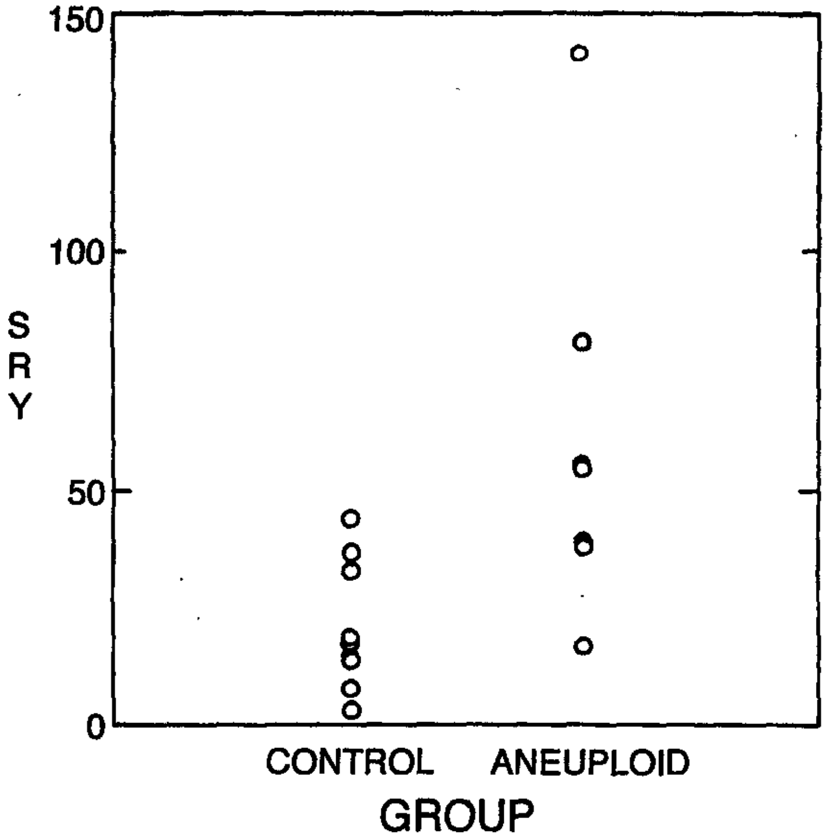
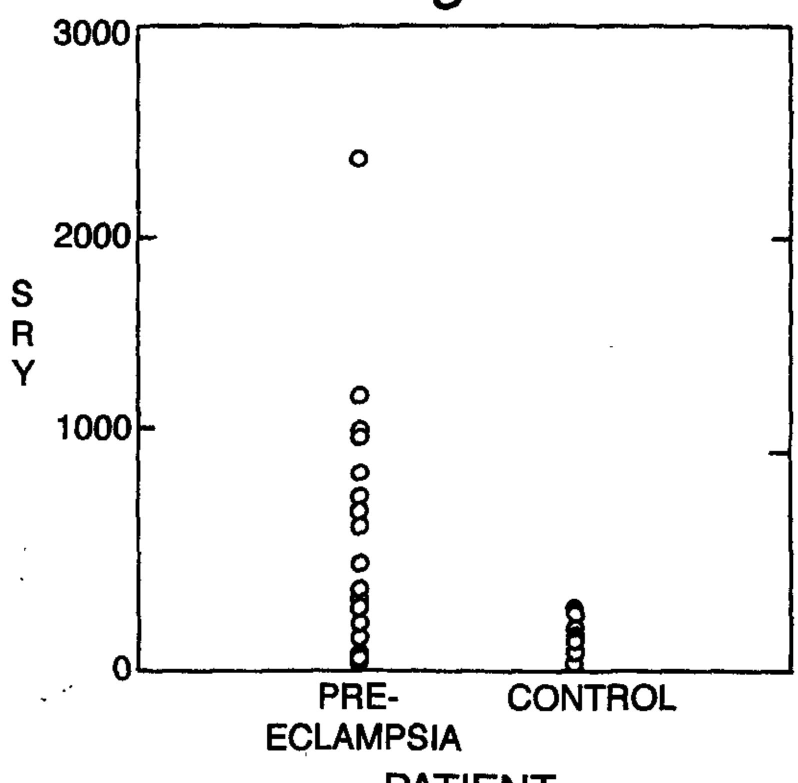


Fig.2.



SUBSTITUTE SHEET (RULE 26)

Fig.3A.

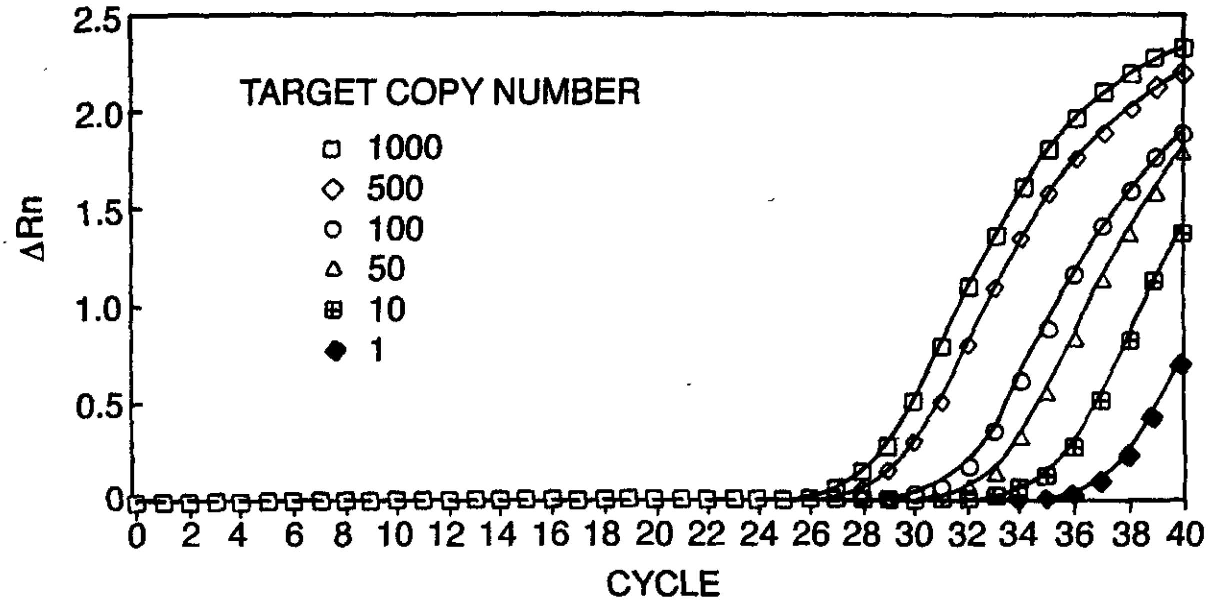
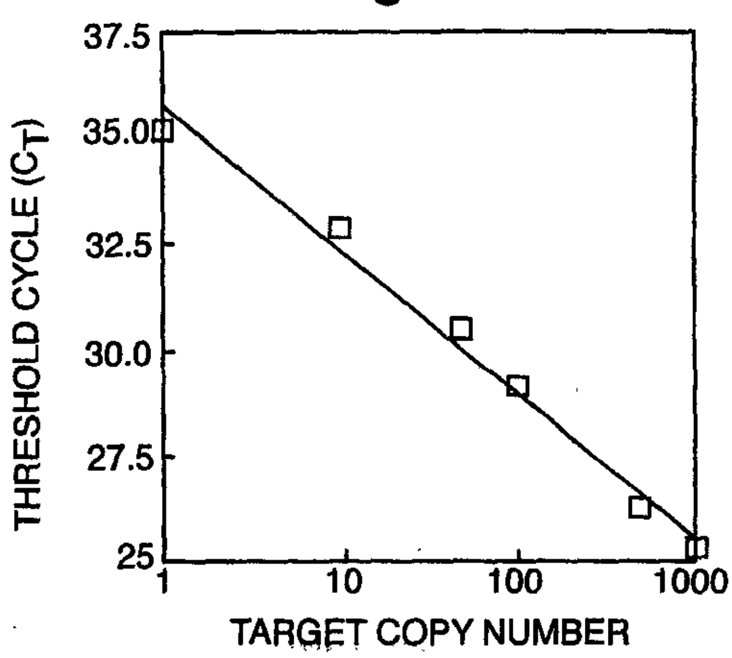


Fig.3B.



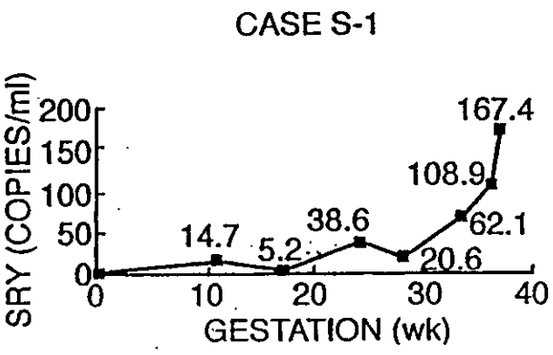


FIG. 4a

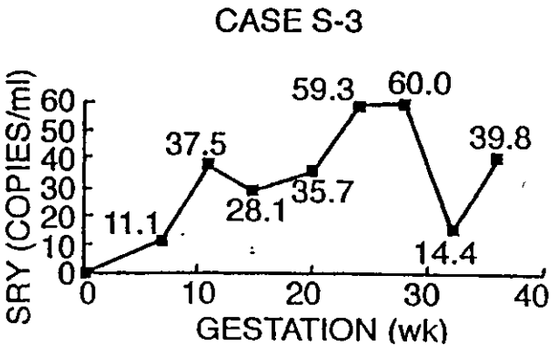


FIG. 4b

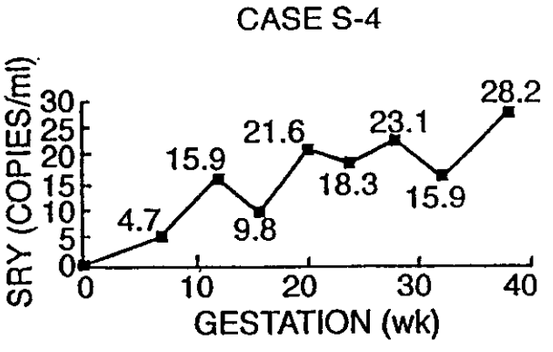


FIG. 4c

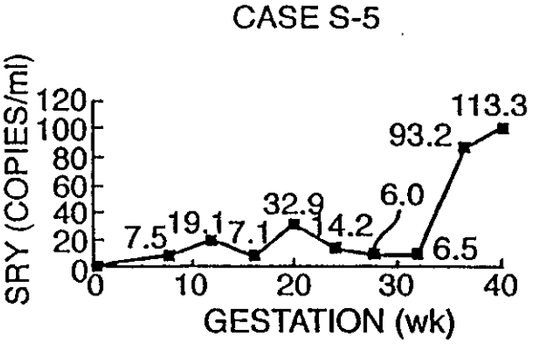


FIG. 4d

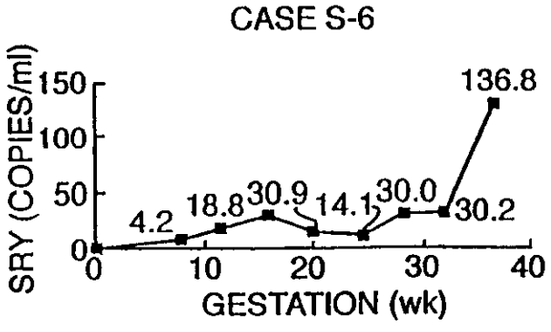


FIG. 4e

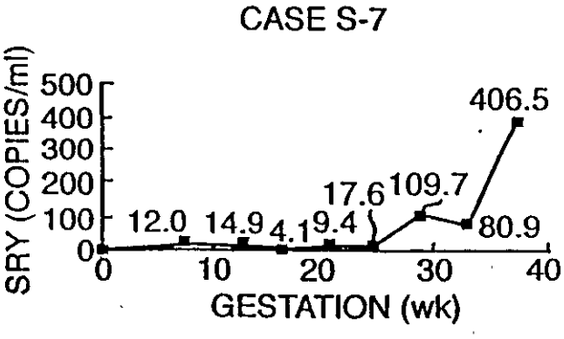


FIG. 4f

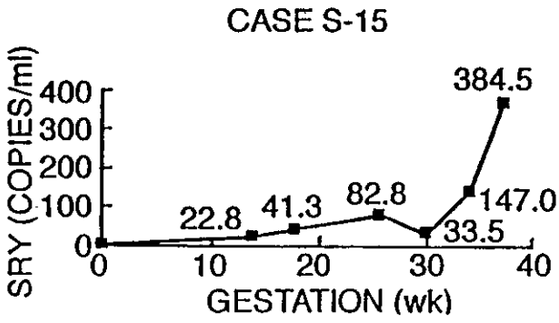


FIG. 4g

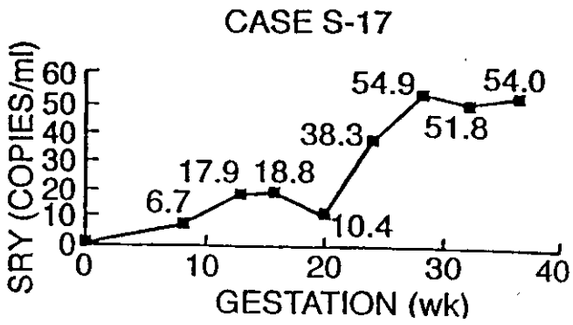


FIG. 4h

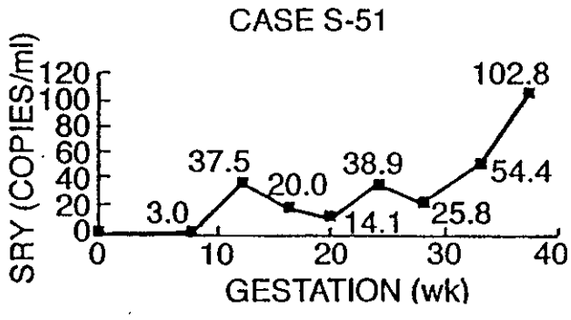


FIG. 4i

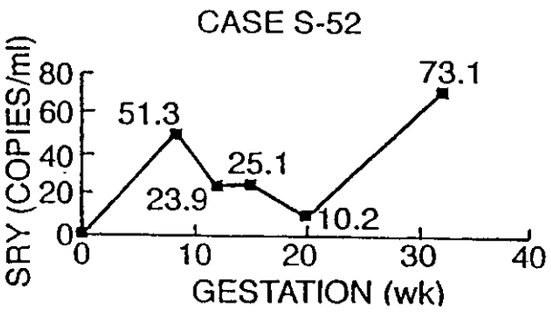


FIG. 4j

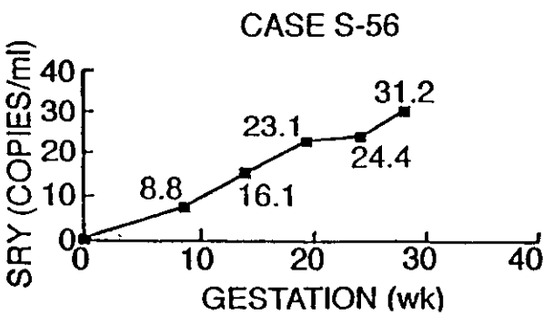


FIG. 4k

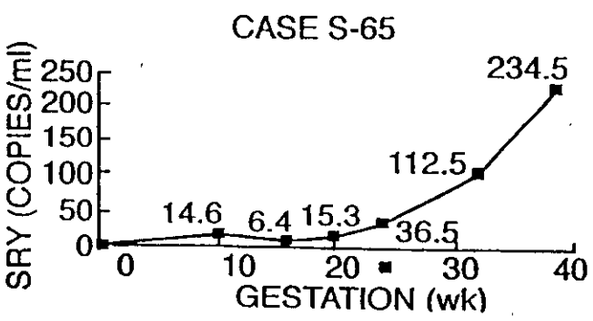


FIG. 4l

#19

UNITED STATES DEPA[illegible]ENT OF COMMERCE
Patent and Trademark [illegible]rice

ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

CHANGE OF ADDRESS/POWER OF ATTORNEY

FILE LOCATION 16X1 SERIAL NUMBER 09380696 PATENT NUMBER 6258540

THE CORRESPONDENCE ADDRESS HAS BEEN CHANGED TO CUSTOMER # 3624

THE PRACTITIONERS OF RECORD HAVE BEEN CHANGED TO CUSTOMER # 3624

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SUITE 400, ONE PENN CENTER
1617 JOHN F. KENNEDY BOULEVARD
PHILADELPHIA PA 19103

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44964 46259 47802 48382

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THIS FILE IS ASSIGNED TO GAU 1655.

PTO-FMD
TALBOT-1/97

(FILE 'HOME' ENTERED AT 12:39:28 ON 29 MAR 2000)

FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE, SCISEARCH' ENTERED AT 12:39:43 ON 29 MAR 2000

L1	3923051	S	SERUM OR PLASMA
L2	821836	S	PRENATAL OR MATERNAL OR FETAL OR FOETAL
L3	136809	S	L1 AND L2
L4	1820	S	L3 AND (PCR OR NUCLEIC ACID)
L5	11088	S	L3 AND (PCR OR NUCLEIC ACID OR DNA)
L6	4454	S	L5 NOT (CALF OR BOVINE)
L7	1746	S	L6 AND (SERUM/TI OR PLASMA/TI OR PRENATAL/TI OR FETAL/TI OR
L8	749		DUPLICATE REMOVE L7 (997 DUPLICATES REMOVED)
L9	541	S	L8 AND (MATERNAL/TI OR FETAL/TI)

(FILE 'HOME' ENTERED AT 13:49:47 ON 14 FEB 2000)

FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE, SCISEARCH' ENTERED AT 13:49:56 ON 14 FEB 2000

E LO/AU
E LO D/AU
L1 17 S E24
E LO DENN/AU
E LO YUK/AU
E LO YUK-MI/AU
E WAINSCOAT/AU
L2 727 S E4-E8
L3 744 S L1 OR L2
L4 314 S L3 AND (NUCLEIC ACID OR DNA)
L5 68 S L4 AND (MATERNAL OR FOETAL OR FETAL)
L6 33 DUPLICATE REMOVE L5 (35 DUPLICATES REMOVED)
L7 8 S L6 AND (SERUM OR PLASMA)

L8 727600 S MATERNAL OR FOETAL OR FETAL
L9 3900005 S SERUM OR PLASMA
L10 132294 S L9 AND L8
L11 503524 S PCR OR POLYMERASE CHAIN
L12 2071 S L10 AND L11
L13 515524 S Y OR DYS14 OR SRY OR RHESUS D
L14 50 S L13 AND L12
L15 28 DUPLICATE REMOVE L14 (22 DUPLICATES REMOVED)
L16 251 S L12 AND (SERUM OR PLASMA)/TI
L17 97 DUPLICATE REMOVE L16 (154 DUPLICATES REMOVED)
L18 71 S L17 NOT (CALF OR BOVINE)
L19 28 S L18 AND (DIAGNOS?)

L9 ANSWER 1 OF 541 MEDLINE
ACCESSION NUMBER: 2000125852 MEDLINE
DOCUMENT NUMBER: 20125852
TITLE: ***Prenatal*** diagnosis of myotonic dystrophy using ***fetal*** ***DNA*** obtained from ***maternal*** ***plasma*** .
AUTHOR: Amicucci P; Gennarelli M; Novelli G; Dallapiccola B
CORPORATE SOURCE: Department of Biopathology and Diagnostic Imaging, Tor Vergata University of Rome, Via Di Tor Vergata 135, 00133 Rome, Italy.
SOURCE: CLINICAL CHEMISTRY, (2000 Feb) 46 (2) 301-2.
Journal code: DBZ. ISSN: 0009-9147.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 200004
ENTRY WEEK: 20000404

L9 ANSWER 5 OF 541 MEDLINE
ACCESSION NUMBER: 2000054918 MEDLINE
DOCUMENT NUMBER: 20054918
TITLE: Rapid ***prenatal*** diagnosis of aneuploidy by quantitative fluorescent ***PCR*** on ***fetal*** samples from mothers at high risk for chromosome disorders.
AUTHOR: Pertl B; Pieber D; Lercher-Hartlieb A; Orescovic I; Haeusler M; Winter R; Kroisel P; Adinolfi M
CORPORATE SOURCE: Department of Obstetrics and Gynecology, University of Graz, Auenbruggerplatz 14, A-8036 Graz, Austria.
SOURCE: MOLECULAR HUMAN REPRODUCTION, (1999 Dec) 5 (12) 1176-9.
Journal code: CWO. ISSN: 1360-9947.
PUB. COUNTRY: ENGLAND: United Kingdom
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY WEEK: 20000303
AB We report the results of a prospective study using quantitative fluorescent polymerase chain reaction (QF- ***PCR***) and small tandem repeat markers (STR) for the rapid ***prenatal*** detection of aneuploidies in a group of pregnant women at increased risk of having fetuses with numerical chromosome disorders. Amniotic fluid samples (n = 52) were collected from mothers undergoing ***prenatal*** invasive testing for ***fetal*** abnormalities on ultrasonographic examination or abnormal ***maternal*** ***serum*** aneuploidy screening results. All samples were tested by cytogenetic analysis, but rapid diagnoses of aneuploidies were offered and performed using QF- ***PCR*** analysis with several STRs specific for chromosomes 21, 18, 13 and X. All cases with numerical chromosome aberrations involving chromosomes 21, 18 and 13 (n = 8) were correctly diagnosed. Three gonosomal aneuplodies (one 47,XXY and two 45,X) were not detected because they were uninformative for the X markers. Another sample with a deletion (46,XX,7q-), that the

present assay was not designed to detect, was not identified. One sample was heavily contaminated with ***maternal*** blood and the results of the QF- ***PCR*** assays were uninformative. The remaining samples from normal fetuses provided QF- ***PCR*** patterns disomic for chromosomes 21, 18, 13 and X. Our study demonstrates that QF- ***PCR*** is a rapid method for the detection of common numerical chromosome disorders and it may play an important role in ***prenatal*** diagnosis for women at high risk for ***fetal*** aneuploidy.

L9 ANSWER 7 OF 541 MEDLINE
ACCESSION NUMBER: 2000039659 MEDLINE
DOCUMENT NUMBER: 20039659
TITLE: ***Fetal*** RhD genotyping from ***maternal*** ***plasma*** .
AUTHOR: Lo Y M
CORPORATE SOURCE: Department of Chemical Pathology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Kong Hong Special Administration Region.. loym@cuhk.edu.hk
SOURCE: ANNALS OF MEDICINE, (1999 Oct) 31 (5) 308-12. Ref: 48
Journal code: AMD. ISSN: 0785-3890.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY WEEK: 20000204
AB The ***prenatal*** diagnosis of ***fetal*** rhesus D (RhD) status is useful for the management of RhD-negative women with partners heterozygous for the RHD gene. Conventional methods for ***prenatal*** ***fetal*** RhD status determination involve invasive procedures such as ***fetal*** blood sampling and amniocentesis. The recent demonstration of the existence of cell-free ***fetal*** ***DNA*** in ***maternal*** ***plasma*** and ***serum*** opens up the possibility of determining ***fetal*** RhD status by analysis of ***maternal*** ***plasma*** or ***serum*** ***DNA*** . This possibility has recently been realized by three independent groups of investigators. This development represents an important step towards the routine application of noninvasive ***fetal*** blood group diagnosis in sensitized pregnancies and may become a model for developing safer noninvasive ***prenatal*** tests for other single-gene disorders.

L9 ANSWER 9 OF 541 MEDLINE
ACCESSION NUMBER: 2000012845 MEDLINE
DOCUMENT NUMBER: 20012845
TITLE: Detection of ***fetal*** -derived paternally inherited X-chromosome polymorphisms in ***maternal*** ***plasma*** .
AUTHOR: Tang N L; Leung T N; Zhang J; Lau T K; Lo Y M
CORPORATE SOURCE: Department of Chemical Pathology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong SAR.
SOURCE: CLINICAL CHEMISTRY, (1999 Nov) 45 (11) 2033-5.
Journal code: DBZ. ISSN: 0009-9147.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 200001
ENTRY WEEK: 20000104

L9 ANSWER 1 OF 541 MEDLINE
ACCESSION NUMBER: 2000125852 MEDLINE
DOCUMENT NUMBER: 20125852
TITLE: ***Prenatal*** diagnosis of myotonic dystrophy using ***fetal*** ***DNA*** obtained from ***maternal*** ***plasma*** .
AUTHOR: Amicucci P; Gennarelli M; Novelli G; Dallapiccola B
CORPORATE SOURCE: Department of Biopathology and Diagnostic Imaging, Tor Vergata University of Rome, Via Di Tor Vergata 135, 00133 Rome, Italy.
SOURCE: CLINICAL CHEMISTRY, (2000 Feb) 46 (2) 301-2.
Journal code: DBZ. ISSN: 0009-9147.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 200004
ENTRY WEEK: 20000404

L9 ANSWER 13 OF 541 MEDLINE
ACCESSION NUMBER: 1999422253 MEDLINE
DOCUMENT NUMBER: 99422253
TITLE: ***Foetal*** RhD genotyping using ***DNA*** extracted from ***maternal*** ***plasma*** .
AUTHOR: Mohan A; Seth S
CORPORATE SOURCE: Department of Emergency Medicine, Sir Venkateswara Institute of Medical Science, Tirupati, Andhra Pradesh.
SOURCE: NATIONAL MEDICAL JOURNAL OF INDIA, (1999 May-Jun) 12 (3) 118-9.
Journal code: BNT. ISSN: 0970-258X.
PUB. COUNTRY: India
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
ENTRY MONTH: 199912
ENTRY WEEK: 19991201

L9 ANSWER 14 OF 541 MEDLINE
ACCESSION NUMBER: 1999402887 MEDLINE
DOCUMENT NUMBER: 99402887
TITLE: Evaluation of different approaches for ***fetal*** ***DNA*** analysis from ***maternal*** ***plasma*** and nucleated blood cells.
AUTHOR: Smid M; Lagona F; de Benassuti L; Ferrari A; Ferrari M; Cremonesi L
CORPORATE SOURCE: Istituto di Rivocero e Cura a Carattere Scientifico, Hospital San Raffaele, Department of Obstetrics and Gynecology, Via Olgettina 60, 20132 Milan, Italy.
SOURCE: CLINICAL CHEMISTRY, (1999 Sep) 45 (9) 1570-2.

Journal code: DBZ. ISSN: 0009-9147.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199911
ENTRY WEEK: 19991104

L9 ANSWER 27 OF 541 MEDLINE
ACCESSION NUMBER: 1999222507 MEDLINE
DOCUMENT NUMBER: 99222507
TITLE: Noninvasive determination of ***fetal*** RhD status using ***fetal*** ***DNA*** in ***maternal*** ***serum*** and ***PCR*** .
AUTHOR: Bischoff F Z; Nguyen D D; Marquez-Do D; Moise K J Jr; Simpson J L; Elias S
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, Texas 77030, USA.. bischoff@bcm.tmc.edu
CONTRACT NUMBER: N01-HD43203 (NICHD)
SOURCE: JOURNAL OF THE SOCIETY FOR GYNECOLOGIC INVESTIGATION, (1999 Mar-Apr) 6 (2) 64-9.
Journal code: CMH. ISSN: 1071-5576.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY WEEK: 19990802
AB OBJECTIVE: Because ***prenatal*** testing of ***fetal*** RhD status by amniocentesis carries small yet finite risks to the fetus and mother, this study sought to determine whether ***fetal*** ***DNA*** in ***maternal*** ***serum*** could be used to detect ***fetal*** RhD status by polymerase chain reaction (***PCR***). METHODS: A retrospective analysis was made of frozen ***serum*** specimens from 20 sensitized RhD-negative pregnant women (ranging from 15.0 to 36.0 weeks' gestation) who were confirmed by serology at birth to have been carrying RhD-positive fetuses. Eleven ***serum*** specimens from RhD-negative individuals served as controls. ***DNA*** was isolated from ***serum*** and used in two ***PCR*** -based methods to detect a 99 base pair (bp) ***DNA*** fragment specific for the RhD gene and a 113 bp fragment specific for the RhCE gene as control. RESULTS: Overall, in 14 (70%) of 20 RhD-positive fetuses the 99 base pair RhD-specific ***PCR*** product was detected. There was no false positive detection among the 11 control ***serum*** specimens. CONCLUSION: The results illustrate the ability to detect ***fetal*** RhD sequences in ***maternal*** ***serum*** of sensitized women. Moreover, the findings demonstrate that ***fetal*** single-gene disorders can be detected prenatally by using ***DNA*** isolated only from ***maternal*** ***serum*** .

L9 ANSWER 33 OF 541 MEDLINE
ACCESSION NUMBER: 1999132218 MEDLINE
DOCUMENT NUMBER: 99132218
TITLE: Quantitative abnormalities of ***fetal*** ***DNA*** in ***maternal*** ***serum*** in preeclampsia [see comments].

COMMENT: Comment in: Clin Chem 1999 Apr;45(4):451-2
AUTHOR: Lo Y M; Leung T N; Tein M S; Sargent I L; Zhang J; Lau T K; Haines C J; Redman C W
CORPORATE SOURCE: Departments of Chemical Pathology, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong SAR.. loym@cuhk.edu.hk
SOURCE: CLINICAL CHEMISTRY, (1999 Feb) 45 (2) 184-8.
Journal code: DBZ. ISSN: 0009-9147.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Cancer Journals; Priority Journals
ENTRY MONTH: 199904
AB BACKGROUND: There is much recent interest in the biologic and diagnostic implication of cell-free non-host ***DNA*** in the ***plasma*** and ***serum*** of human subjects. To determine if quantitative abnormalities of circulating non-host ***DNA*** may be associated with certain pathologic processes, we used circulating ***fetal*** ***DNA*** in preeclampsia as a model system. METHODS: We studied 20 preeclamptic women and 20 control subjects of comparable gestational age (means, 32 and 33 weeks, respectively). Male ***fetal*** ***DNA*** in ***maternal*** ***serum*** was measured using real-time quantitative ***PCR*** for the SRY gene on the Y chromosome. RESULTS: The imprecision (CV) of the assay was 2.7%. The median circulating ***fetal*** ***DNA*** was increased fivefold in 20 preeclamptic women compared with 20 control pregnant women (381 vs 76 genome-equivalents/mL, P <0.001). CONCLUSIONS: These observations suggest that preeclampsia is associated with disturbances in the liberation and/or clearance mechanisms of circulating ***DNA*** . These results also raise the possibility that measurement of circulating ***DNA*** may prove useful as a marker for the diagnosis and/or monitoring of preeclampsia.

L9 ANSWER 36 OF 541 MEDLINE
ACCESSION NUMBER: 1999115099 MEDLINE
DOCUMENT NUMBER: 99115099
TITLE: Rapid clearance of ***fetal*** ***DNA*** from ***maternal*** ***plasma*** .
AUTHOR: Lo Y M; Zhang J; Leung T N; Lau T K; Chang A M; Hjelm N M
CORPORATE SOURCE: Department of Chemical Pathology, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong.
SOURCE: AMERICAN JOURNAL OF HUMAN GENETICS, (1999 Jan) 64 (1) 218-24.
Journal code: 3IM. ISSN: 0002-9297.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY WEEK: 19990502
AB ***Fetal*** ***DNA*** has been detected in ***maternal*** ***plasma*** during pregnancy. We investigated the clearance of circulating ***fetal*** ***DNA*** after delivery, using quantitative ***PCR*** analysis of the sex-determining region Y gene as a marker for male fetuses. We analyzed ***plasma*** samples from 12

women 1-42 d after delivery of male babies and found that circulating ***fetal*** ***DNA*** was undetectable by day 1 after delivery. To obtain a higher time-resolution picture of ***fetal*** ***DNA*** clearance, we performed serial sampling of eight women, which indicated that most women (seven) had undetectable levels of circulating ***fetal*** ***DNA*** by 2 h postpartum. The mean half-life for circulating ***fetal*** ***DNA*** was 16.3 min (range 4-30 min). ***Plasma*** nucleases were found to account for only part of the clearance of ***plasma*** ***fetal*** ***DNA*** . The rapid turnover of circulating ***DNA*** suggests that ***plasma*** ***DNA*** analysis may be less susceptible to false-positive results, which result from carryover from previous pregnancies, than is the detection of ***fetal*** cells in ***maternal*** blood; also, rapid turnover may be useful for the monitoring of feto- ***maternal*** events with rapid dynamics. These results also may have implications for the study of other types of nonhost ***DNA*** in ***plasma*** , such as circulating tumor-derived and graft-derived ***DNA*** in oncology and transplant patients, respectively.

L9 ANSWER 41 OF 541 MEDLINE
ACCESSION NUMBER: 1999049885 MEDLINE
DOCUMENT NUMBER: 99049885
TITLE: ***Prenatal*** diagnosis of ***fetal*** RhD status by molecular analysis of ***maternal*** ***plasma*** [see comments].
COMMENT: Comment in: N Engl J Med 1998 Dec 10;339(24):1775-7
AUTHOR: Lo Y M; Hjelm N M; Fidler C; Sargent I L; Murphy M F; Chamberlain P F; Poon P M; Redman C W; Wainscoat J S
CORPORATE SOURCE: Department of Chemical Pathology, Chinese University of Hong Kong, Prince of Wales Hospital.
SOURCE: NEW ENGLAND JOURNAL OF MEDICINE, (1998 Dec 10) 339 (24) 1734-8.
Journal code: NOW. ISSN: 0028-4793.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199902
ENTRY WEEK: 19990204
AB BACKGROUND: The ability to determine ***fetal*** RhD Status noninvasively is useful in the treatment of RhD-sensitized pregnant women whose partners are heterozygous for the RhD gene. The recent demonstration of ***fetal*** ***DNA*** in ***maternal*** ***plasma*** raises the possibility that ***fetal*** RhD genotyping may be possible with the use of ***maternal*** ***plasma*** . METHODS: We studied 57 RhD-negative pregnant women and their singleton fetuses. ***DNA*** extracted from ***maternal*** ***plasma*** was analyzed for the RhD gene with a fluorescence-based polymerase-chain-reaction (***PCR***) test sensitive enough to detect the RhD gene in a single cell. ***Fetal*** RhD status was determined directly by serologic analysis of cord blood or ***PCR*** analysis of amniotic fluid. RESULTS: Among the 57 RhD-negative women, 12 were in their first trimester of pregnancy, 30 were in their second trimester, and 15 were in their third trimester. Thirty-nine fetuses were RhD-positive, and 18 were RhD-negative. In the samples obtained from women in their second or third trimester of

pregnancy, the results of RhD ***PCR*** analysis of ***maternal*** ***plasma*** ***DNA*** were completely concordant with the results of serologic analysis. Among the ***maternal*** ***plasma*** samples collected in the first trimester, 2 contained no RhD ***DNA*** , but the fetuses were RhD-positive; the results in the other 10 samples were concordant (7 were RhD-positive, and 3 RhD-negative). CONCLUSIONS: Noninvasive ***fetal*** RhD genotyping can be performed rapidly and reliably with the use of ***maternal*** ***plasma*** beginning in the second trimester of pregnancy.

L9 ANSWER 44 OF 541 MEDLINE
ACCESSION NUMBER: 1998449274 MEDLINE
DOCUMENT NUMBER: 98449274
TITLE: Detection of ***fetal*** RHD-specific sequences in ***maternal*** ***plasma*** [letter].
AUTHOR: Faas B H; Beuling E A; Christiaens G C; von dem Borne A E; van der Schoot C E
SOURCE: LANCET, (1998 Oct 10) 352 (9135) 1196.
Journal code: L0S. ISSN: 0140-6736.
PUB. COUNTRY: ENGLAND: United Kingdom
Letter
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199901
ENTRY WEEK: 19990104

L9 ANSWER 56 OF 541 MEDLINE
ACCESSION NUMBER: 1998198334 MEDLINE
DOCUMENT NUMBER: 98198334
TITLE: Quantitative analysis of ***fetal*** ***DNA*** in ***maternal*** ***plasma*** and ***serum*** : implications for noninvasive ***prenatal*** diagnosis.
AUTHOR: Lo Y M; Tein M S; Lau T K; Haines C J; Leung T N; Poon P M; Wainscoat J S; Johnson P J; Chang A M; Hjelm N M
CORPORATE SOURCE: Department of Chemical Pathology, The University of Hong Kong, Prince Wales Hospital, Shatin, New Territories, Hong Kong.. loym@cuhk.edu.hk
SOURCE: AMERICAN JOURNAL OF HUMAN GENETICS, (1998 Apr) 62 (4) 768-75.
Journal code: 3IM. ISSN: 0002-9297.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY WEEK: 19980802
AB We have developed a real-time quantitative ***PCR*** assay to measure the concentration of ***fetal*** ***DNA*** in ***maternal*** ***plasma*** and ***serum*** . Our results show that ***fetal*** ***DNA*** is present in high concentrations in ***maternal*** ***plasma*** , reaching a mean of 25.4 genome equivalents/ml (range 3.3-69. 4) in early pregnancy and 292.2 genome equivalents/ml (range 76. 9-769) in late pregnancy. These concentrations correspond to 3.4% (range 0.39%-11.9%) and 6.2% (range 2.33%-11.4%) of the total ***plasma*** ***DNA*** in early and late pregnancy, respectively. Sequential

follow-up study of women who conceived by in vitro fertilization shows that ***fetal*** ***DNA*** can be detected in ***maternal*** ***serum*** as early as the 7th wk of gestation and that it then increases in concentration as pregnancy progresses. These data suggest that ***fetal*** ***DNA*** can be readily detected in ***maternal*** ***plasma*** and ***serum*** and may be a valuable source of material for noninvasive ***prenatal*** diagnosis.

L9 ANSWER 57 OF 541 MEDLINE
ACCESSION NUMBER: 1998198332 MEDLINE
DOCUMENT NUMBER: 98198332
TITLE: ***Fetal*** ***DNA*** in ***maternal*** ***plasma*** : the plot thickens and the placental barrier thins [editorial].
AUTHOR: Bianchi D W
SOURCE: AMERICAN JOURNAL OF HUMAN GENETICS, (1998 Apr) 62 (4) 763-4. Ref: 13
Journal code: 3IM. ISSN: 0002-9297.
PUB. COUNTRY: United States
Editorial
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY WEEK: 19980802

L9 ANSWER 74 OF 541 MEDLINE
ACCESSION NUMBER: 97420079 MEDLINE
DOCUMENT NUMBER: 97420079
TITLE: Presence of ***fetal*** ***DNA*** in ***maternal*** ***plasma*** and ***serum*** .
AUTHOR: Lo Y M; Corbetta N; Chamberlain P F; Rai V; Sargent I L; Redman C W; Wainscoat J S
CORPORATE SOURCE: Nuffield Department of Clinical Biochemistry, John Radcliffe Hospital, University of Oxford, UK.
SOURCE: LANCET, (1997 Aug 16) 350 (9076) 485-7.
Journal code: L0S. ISSN: 0140-6736.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199711
ENTRY WEEK: 19971103
AB BACKGROUND: The potential use of ***plasma*** and ***serum*** for molecular diagnosis has generated interest. Tumour ***DNA*** has been found in 'the ***plasma*** and ***serum*** of cancer patients, and molecular analysis has been done on this material. We investigated the equivalent condition in pregnancy-that is, whether ***fetal*** ***DNA*** is present in ***maternal*** ***plasma*** and ***serum*** . METHODS: We used a rapid-boiling method to extract ***DNA*** from ***plasma*** and ***serum*** . ***DNA*** from ***plasma*** , ***serum*** , and nucleated blood cells from 43 pregnant women underwent a sensitive Y- ***PCR*** assay to detect circulating male ***fetal*** ***DNA*** from women bearing male

fetuses. FINDINGS: Fetus-derived Y sequences were detected in 24 (80%) of the 30 ***maternal*** ***plasma*** samples, and in 21 (70%) of the 30 ***maternal*** ***serum*** samples, from women bearing male fetuses. These results were obtained with only 10 microL of the samples. When ***DNA*** from nucleated blood cells extracted from a similar volume of blood was used, only five (17%) of the 30 samples gave a positive Y signal. None of the 13 women bearing female fetuses, and none of the ten non-pregnant control women, had positive results for ***plasma*** , ***serum*** or nucleated blood cells. INTERPRETATION: Our finding of circulating ***fetal*** ***DNA*** in ***maternal*** ***plasma*** may have implications for non-invasive ***prenatal*** diagnosis, and for improving our understanding of the fetomaternal relationship.

PATENT APPLICATION FEE DETERMINATION RECORD

Effective November 10, 1998

Application or Docket Number: 09/380696

CLAIMS AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA
BASIC FEE		
TOTAL CLAIMS	26 minus 20=	* 6
INDEPENDENT CLAIMS	3 minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
420	~~380.00~~	OR		840
X$ 9=	54	OR	X$18=	108
X39=		OR	X78=	
+130=		OR	+260=	
TOTAL	474	OR	TOTAL	948

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
13				
Total	* 27	Minus	** 26	= 1
Independent	* 3	Minus	*** 3	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	18
X39=		OR	X78=	
+130=		OR	+260=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	paid

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X39=		OR	X78=	
+130=		OR	+260=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X39=		OR	X78=	
+130=		OR	+260=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Form PTO 1130
(REV 2/94)

PACE DATA ENTRY CODING SHEET

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

1ST EXAMINER	V. Wallace	DATE	
2ND EXAMINER		DATE	10/21/99

APPLICATION NUMBER	TYPE APPL	FILING DATE (MONTH DAY YEAR)	SPECIAL HANDLING	GROUP ART UNIT	CLASS	SHEETS OF DRAWING
09/380696	1	11 29 99	0	1623	536	4

TOTAL CLAIMS	INDEPENDENT CLAIMS	SMALL ENTITY?	FILING FEE	FOREIGN LICENSE	ATTORNEY DOCKET NUMBER
26	3	0	1096	Y	SHP-PT048

CONTINUITY DATA

CONT CODE	STATUS CODE	PARENT APPLICATION SERIAL NUMBER	PCT APPLICATION SERIAL NUMBER	PARENT PATENT NUMBER	PARENT FILING DATE (MONTH DAY YEAR)
			PCT / /		
			PCT / /		
			PCT / /		
			PCT / /		
			PCT / /		

PCT/FOREIGN APPLICATION DATA

FOREIGN PRIORITY CLAIMED	COUNTRY CODE	PCT/FOREIGN APPLICATION SERIAL NUMBER	FOREIGN FILING DATE (MONTH DAY YEAR)
Y	GBB	9704444,0	03 04 97

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

(FOR USE WITH FORM PTO-875)

SERIAL NO.

FILING DATE

APPLICANT(S) 09/380696

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1	1					
2		1				
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TOTAL IND.	3					
TOTAL DEP.	23					
TOTAL CLAIMS	26					

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TOTAL IND.						
TOTAL DEP.						
TOTAL CLAIMS						

PTO-1360 (3-78)

**MAY BE USED FOR ADDITIONAL CLAIMS OR AMENDMENTS*

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